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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/543,078	07/21/2005	Michinori Kohara	382.1047	7140

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EXAMINER	
PITRAK, JENNIFER S	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/543,078	KOHARA ET AL.	
	Examiner	Art Unit	
	JENNIFER PITRAK	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 April 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7-12,14-16 and 18* is/are pending in the application.

4a) Of the above claim(s) *9,10,14 and 15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7,8,11,12,16 and 18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/28/10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Remarks

The amendments and arguments filed 04/28/2010 have been entered and considered. Claims 7-12, 14-16, and 18 are pending. Claims 9, 10, 14 and 15 are withdrawn from further consideration as being drawn to a nonelected invention. Claims **7, 8, 11, 12, 16, and 18** are under examination insofar as they are directed to SEQ ID NO:23.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Any rejections or objections previously presented but not restated herein are withdrawn.

Objection to the Specification and Drawings - maintained

(Sequence Compliance)

The amendment to the specification with regard to Figure 4 does not render the specification compliant with 37 CFR 1.821-1.825. SEQ ID NOs 1-11 are recited in the descriptions for Figures 4A, 4B, and 4C, but the corresponding nucleotide sequences are not identified.

Claim Rejections - 35 USC § 102 - withdrawn

The rejection of claims 7, 8, and 18 under 35 U.S.C. 102(b) as being anticipated by Elbashir, et al. 2002 (Methods, v.26:199-213) is withdrawn. The claim amendments have obviated the rejection.

The rejection of claims 7, 8, 11, and 18 under 35 U.S.C. 102(a) as being anticipated by Yu, et al. (2002, PNAS, v.99:6047-52, of record) ("Yu") is withdrawn. The claim amendments have obviated the rejection.

The rejection of claims 7, 11, 12, and 16 under 35 U.S.C. 102(e) as being anticipated by Jadhav, et al. (US 2005/0209180, of record) ("Jadhav") is withdrawn. The claim amendments have obviated the rejection.

Claim Rejections - 35 USC § 102 - maintained

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 8 and 18 are rejected under 35 U.S.C. 102(e) as being anticipated by Jadhav, et al. (US 2005/0209180, of record) ("Jadhav"). This rejection is maintained.

The claims are to an siRNA having a nucleotide sequence which hybridizes under stringent conditions with an RNA region of HCV having a sequence complementary to a nucleotide sequence shown in SEQ ID NO:23 and to an siRNA having the nucleotide sequence SEQ ID NO: 23 wherein 7 or fewer nucleotides are deleted, substituted, or added and being able to hybridize with the RNA of HCV. Absent evidence to the contrary, an siRNA meeting the structural limitations of the claims is presumed to inhibit HCV replication.

Jadhav teaches siRNAs targeting HCV for the treatment of HCV-related diseases and conditions (page 1, paragraph 2; page 3, paragraph 14). Jadhav teaches an siRNA comprising a sense strand having SEQ ID NO:298 and an antisense strand having SEQ ID NO:994. This siRNA comprises 18 nucleotides (underlined) of the instantly claimed SEQ ID NO:23 as shown (Table II on page 82).

```
SEQ ID NO:23              5′-gucucguagaccgugcauca - 3′

Jadhav SEQ ID NO:298      5′-gucucguagaccgugcacc -3′
                             ||||||||||||||||||
Jadhav SEQ ID NO:994      3′-cagagcaucuggcacgugg - 5′
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Such an siRNA would hybridize under stringent conditions with an RNA region of HCV having a sequence complementary to SEQ ID NO: 23. Such an siRNA has the sequence shown in SEQ ID NO: 23 with one nucleotide substituted and one nucleotide deleted. Thus, Jadhav clearly anticipates the instant claims.

Response to relevant arguments

Applicant argues that the Jadhav reference has 17 nucleotides and does not have the three nucleotides at the 3' end of SEQ ID NO: 23 of the instant invention (p.10 of arguments). This is

not persuasive because Jadhav teaches an siRNA that meets the instant claim limitations as indicated in the above rejection.

Claim Rejections - 35 USC § 103-maintained

Claims 7, 8, 11, 12, 16, and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Seki, *et al.* (1994, CA2104649, of record)("Seki"), Bass (2001, Nature v.411:428-429, of record)("Bass"), and Yu, et al. (2002, PNAS, v.99:6047-52, of record)("Yu"). This rejection is maintained.

The claims are to an siRNA having the nucleotide sequence SEQ ID NO:23 or to an siRNA having a nucleotide sequence that hybridizes under stringent conditions with an RNA region of HCV having a sequence complementary to the nucleotide sequence, SEQ ID NO:23, and to vectors comprising the siRNAs. Claims 12 and 16 are directed to a therapeutic agent for hepatitis C wherein the active ingredient is the siRNA of claim 7. Absent evidence to the contrary, an siRNA meeting the structural limitations of claim 7 is presumed to perform as a therapeutic agent for hepatitis C.

Seki teaches an antisense nucleotide targeting HCV and complementary to 19 out of 20 nucleotides of SEQ ID NO:23 and that is 20 nucleotides in length. Seki discloses antisense oligonucleotides useful as antiviral agents (see abstract) and particularly discloses SEQ ID NO:83, which is complementary to nucleotides 2-20 of the instant SEQ ID NO:23 (pages 32-35).

```
SEQ ID NO:23          5′-GUCUCGUAGACCGUGCAUCA - 3′
SEKI SEQ ID NO: 83     3'-AGAGCATCTGGCACGTAGTA - 5'
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Seki does not teach siRNAs. Seki does not teach siRNAs in vectors.

Bass teaches on page 429, first column, that RNA interference is a routinely used gene silencing technique that has proven to be more robust than antisense techniques by working more often, decreasing expression to lower levels than antisense oligonucleotides, and working at concentrations several orders of magnitude below the concentrations typically used in antisense experiments.

Yu teaches that siRNAs are 21-nucleotide RNA duplexes that can be expressed from a vector and that synthesis of siRNAs from an expression vector is an economical alternative to chemical synthesis and that vector-expressed siRNAs may be more practical for *in vivo* use of siRNAs, such as in intact animals and for gene therapy (abstract; p.6051, first paragraph of "Discussion"; page 6052, last paragraph).

It would have been obvious to one of ordinary skill in the art at the time of invention to make an siRNA (double-stranded RNA) targeting the region of HCV corresponding to SEQ ID NO:23 for the purpose of reducing HCV expression and to express the siRNA from a vector. This would have been obvious because Seki teaches antisense oligonucleotides that target most of the instantly claimed SEQ ID NO:23. Bass provides a motivation to make a double-stranded RNA (siRNAs) instead of an antisense oligonucleotide by teaching that RNA interference is more robust than antisense techniques by decreasing expression to lower levels and working at much lower concentrations than antisense. Based on the motivation provided by Bass to use double-stranded RNA instead of antisense compounds to down-regulate target gene expression, one of ordinary skill in the art would recognize that targeting HCV with an siRNA corresponding to SEQ ID NO:23 would be more effective agent than targeting HCV with the antisense taught by Seki. It would have been obvious to make the siRNA having 21 nucleotides in each strand

because Bass and Yu teach that siRNAs are 21-nt-long duplexes. Extension of the sequence taught by Seki et al by one nucleotide in either direction, 3' or 5', would be obvious to do in order to make an siRNA having 21 nucleotides. One of ordinary skill in the art would have had a reasonable expectation of success in making and using an siRNA to reduce HCV expression because Bass teaches RNAi using dsRNA is a more specific and more potent method than antisense. Yu provides a reason to express siRNAs from vectors be teaching that such expression is more economical than chemical siRNA synthesis and may be more practical than using chemically-synthesized siRNAs for *in vivo* applications. Thus, the invention of claims 7, 8, 11, 12, 16, and 18 would have been obvious, as a whole, at the time of filing of the instant application.

Response to arguments

Applicant argues that the Seki reference does not provide any experimental result or data supporting the effectiveness of the nucleotide of SEQ ID No. 83 (SMS 19). Applicant argues that Seki reference at page 57 discounts the effectiveness of the nucleotide of SEQ ID No. 83 (SMS 19). This is not persuasive. At pages 32-34, Seki explains that the antisense compounds synthesized in Example 3, which include SMS 19 (SEQ ID NO:83), were effective in inhibiting HCV. Particularly effective were those oligonucleotides targeting the region of SEQ ID NO: 1 from positions 355-359. As Applicant has noted, SEQ ID NO: 83 is targeted to SEQ ID NO: 1 from positions 351-370.

Applicant then argues that that the Seki reference provides a disincentive for those of skill in the art to use SEQ ID NO: 83 because its sequence overlaps with that of "Anti-3", which supposedly exhibits non-specific effects. Applicant refers to the English translation of JP patent

publication No. H06-311885, but did not provide the reference. This argument is not persuasive because, as indicated in the preceding paragraph, SEQ ID NO: 83 inhibited HCV and because siRNA- and antisense-mediated target inhibition operate via distinct mechanisms, such that non-specific effects cannot be presumed to carry over from one mechanism to the other. One of skill in the art would be motivated to make siRNA corresponding to any or all of the targets taught by Seki, et al. with a reasonable expectation of success given that siRNAs were known to be more effective than antisense oligonucleotides at inhibiting target expression.

Applicant then argues that the Bass reference is silent about the relationship between a nucleotide sequence of an siRNA and that of an antisense DNA and that therefore one of skill would not expect that an siRNA having a nucleotide sequence complementary to a known antisense DNA is more effective than antisense DNA. This is not persuasive. While one of skill may not know whether an siRNA having a nucleotide sequence complementary to a known antisense DNA is more effective than antisense DNA, one of skill would certainly be motivated to make siRNAs to the same target gene and would be motivated to use target sequences that were already known in the art. Bass provides a reasonable expectation that an siRNA corresponding to a known antisense DNA will be effective in inhibiting the target.

Applicant finally argues that the Yu reference does not teach or suggest the instantly claimed sequence. This is not persuasive because Yu is relied upon for the teaching of expressing siRNA from a vector, not for the sequence.

Double Patenting - withdrawn

The provisional rejection of claims 11 and 16 is withdrawn because the claim amendments have obviated the rejection.

Double Patenting - New

Claims 11 and 16 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 16-18, 25 and 26 of copending Application No. 10/567168 in view of Seki, *et al.* (1994, CA2104649, of record)("Seki"), Bass (2001, Nature v.411:428-429, of record)("Bass"), and Yu, et al. (2002, PNAS, v.99:6047-52, of record)("Yu").

This is a provisional obviousness-type double patenting rejection.

The instant claims are to a vector comprising an HCV-targeted siRNA molecule having a sequence of SEQ ID NO:23.

The claims of Application No. 10/567168 are to a dumbbell-shaped DNA vector encoding an siRNA targeting HCV. The application does not teach a vector comprising an siRNA having the sequence of the instant SEQ ID NO:23.

Seki, Bass, and Yu provide the teachings, suggestions, and motivation to make vectors comprising siRNAs targeted to HCV having the instant SEQ ID NO: 23 as indicated in the rejection under 35 USC §103, above.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JENNIFER PITRAK whose telephone number is (571)270-3061. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Fereydoun Sajjadi can be reached on 571-272-3311. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jennifer Pitrak
Examiner
Art Unit 1635

/Richard Schnizer/
Primary Examiner, Art Unit 1635